SECTION 2. RESULTS

1. Results of recruitment

1.1 Participating specialty centres

A total of 382 specialty centres (neurology, internal medicine, endocrinology, rheumatology, dermatology, paediatrics) were asked to report autoimmune disorders cases in PGRx (all gender and age groups), of which 299 recruited at least one patient with an autoimmune disorder. Of them, 168 collected autoimmune disorders cases in 11-25 y.o females meeting all inclusion and exclusion criteria for this study, and were employed to be part of this PGRx Cervarix®– autoimmune disorders study.

Table 1. Specialty centres participating in the PGRx network and participation in the Cervarix®-Autoimmune disorders Study

		Date of first inclusion	Centres who recruited at least one patient (all PGRx network) n	Centres who recruited at least one eligible patient for this study n
Total	*		299	168
Group 1	CD/MS	08/11/2007	43	22
Group 2	CTD	02/04/2008	71	40
Group 3	GBS	11/02/2008	31	9
Group 4	AIT	22/04/2008	48	30
Group 4	T1D	08/04/2008	54	36
Group 5	ITP	01/04/2008	52	31

*CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura.

The distribution of recruiting centres per type is shown in the table below.

Table 2. Distribution of recruiting centres per type

PGRx Centres	Teaching hospital	Non-teaching hospital	Private Hospital
CD/MS	73%	27%	0%
CTD	78%	20%	2%
GBS	78%	22%	0%
AIT	35%	41%	24%
T1D	47%	47%	6%
ITP	91%	9%	0%
All	**65%**	**28%**	**7%**

*CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura.

Centres were distributed throughout France (see map with Figure 1).

Figure 1. Distribution of PGRx network of specialist centres in France

1.2. Participating General Practice centres

A total of 406 General practice settings participate at least once in PGRx, among whom 236 collected during the study period at least one eligible referent for this study (11-25 y.o females meeting all inclusion and exclusion criteria (Table 2) and were employed to be part of this PGRx Cervarix®– autoimmune disorders study.

Table 3. General practice centres in PGRx and participation in the Cervarix®-Autoimmune disorders Study

	Date of first inclusion	GP practices in PGRx (at least once)	GP practices who recruited at least 1 eligible referent (11-25 y.o female meeting inclusion/exclusion criteria)
GP practice active	27/03/2007	406	236

The GP practices were distributed all over the country and covered all regions where cases were recruited (see Map with Figure 2).

Figure 2. Distribution of PGRx general practice settings in France (n=406)

1.3 Recruitment of cases

1.3.1 Periods of recruitment

Only patients with index date from the 1st of April 2008 were included as the transparency committee authorised the reimbursement of Cervarix® on March 5th, 2008. The data set used for the analysis was from the October 13, 2014 on patients included until September 26, 2014 (inclusive) after last data clarifications were received.

1.3.2. Target numbers of cases to be recruited

The target numbers of cases to be recruited for each disease was defined a priori (in the protocols), based on the usual annual recruitment of such disorders in the participating centres (as declared by the centres and/or observed in PGRx before). The targets were sets for 3-year recruitment period (according to recruitment periods stipulated by French health authorities in relation to reports of monitoring). An extended period of recruitment was agreed with GSK, a second 3-year recruitment period was added due to very low rate of exposure to Cervarix® in the reference pool during the first 3-year recruitment period.

For all autoimmune autoimmune disorders in 11-25 years old females combined, the target recruitment was 624 cases (table 4). The targets for each individual autoimmune disorder were also set (table 4). They had been set at 25 cases of central demyelination per year, 30 cases of connective tissue diseases (lupus, rheumatoid arthritis, myositis or dermatomyositis) per year, 3 then 5 cases of Guillain Barré Syndroms per year, 15 Type 1 diabetes mellitus per year, 15 autoimmune thyroid disorders (AITD, including Grave's disease and Hashimoto disease and other autoimmune thyroiditis) per year, 15 idiopathic thrombocytopenic puprpura (ITP) per year.

1.3.3. Recruitments

Table 4 also displays the recruitments for all autoimmune disorders combined and for each disorder.

Five hundred sixty nine (569) eligible incident cases were recruited, among whom 511 could be interviewed (Table 4). The table also reports the total number of incident AID cases recruited (all age and gender groups) in the PGRx network.

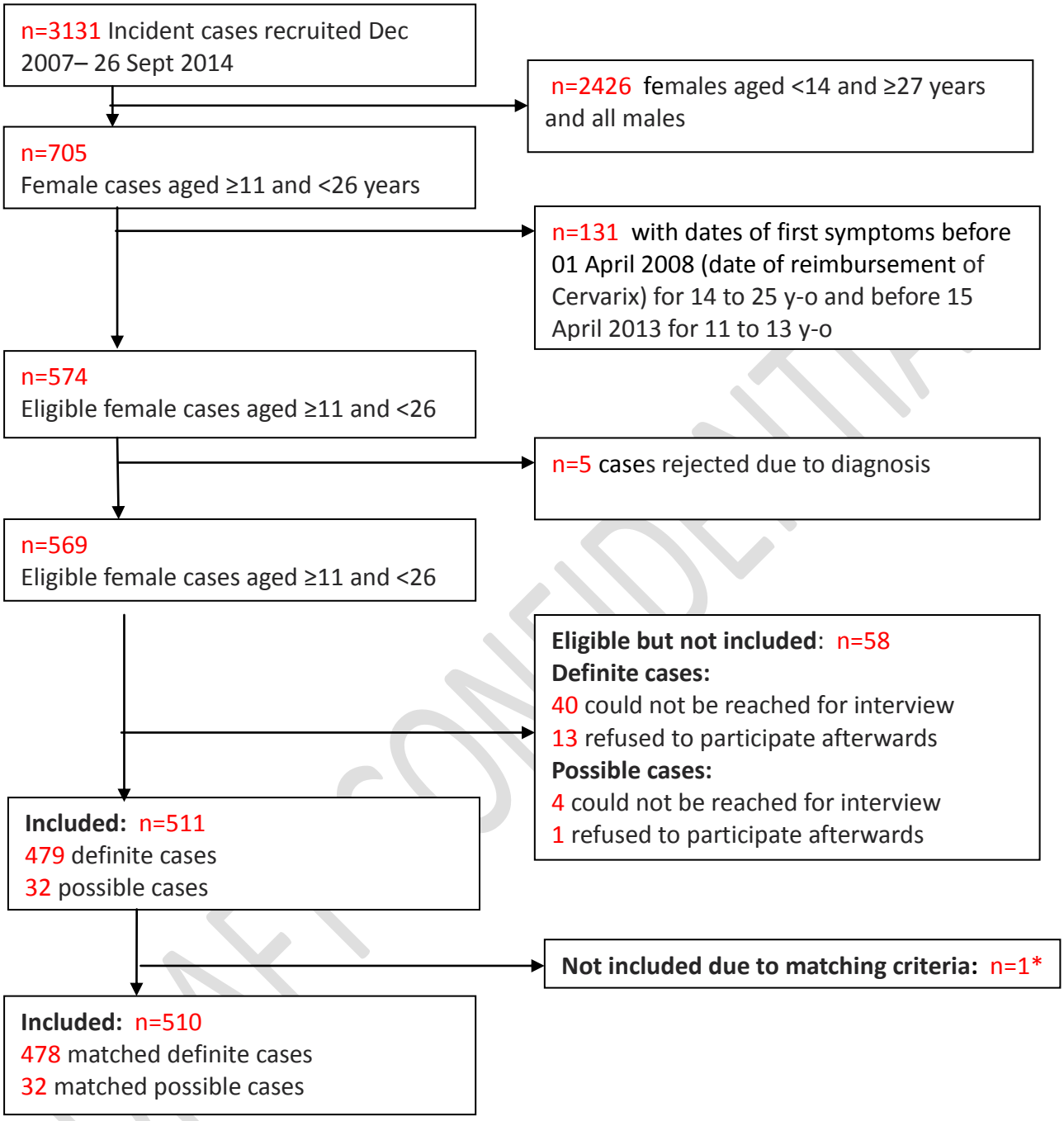
Table 4. Recruitment of first autoimmune disorders cases

Patients	Incident cases (all group all age)	Targeted females 11-25 yrs over 6 years	Reported females 11-25 yrs	Eligible females 11-25 yrs	Interviewed*	Interviewed ('success rate')
	n	n	n	n	n	%
All AID	**3131**	**624**	**705**	**569**	**511**	**90%**
CD/MS	694	150	160	129	116	90%
CTD	538	180	139	116	105	91%
GBS	283	24	16	13	13	100%
T1D	410	90	136	100	94	94%
AIT	522	90	144	121	106	88%
ITP	684	90	110	90	77	86%

*CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura.
*or parents interviewed

Figure 3 describes the flowchart of recruitment and inclusion/exclusion in the study, as well as matching, for all autoimmune disorders combined. The flow charts for each individual disorder are appended.

Figure 3. Flow chart showing recruitment of all studied autoimmune cases used in the combined analysis



*This case could also not be matched for the study of each disorder separately, female T1D case aged 11.2 year-old categorised as definite case.

During the study period (occurrence afetr April 1st, 2008 for cases aged from 14 to 25 years-old and after April 15th, 2013 for cases aged from 11 to 25 years-old), PGRx Network centres recruited 574 females aged 11 to 25 years inclusive, with suspected autoimmune disorder. 5 were rejected as they did not meet the case definition (they are described in detail in table 5). 569 recruited patients had definite or possible diagnoses, 58 could not be interviewed; these non-interviewed cases are described further below. After matching, 510 case patients were included in the analysis of all autoimmune disorders combined, of which 418 case patients were with definite diagnoses and 92 with possible diagnoses.
This case could also not be matched for the study of each disorder separately.

1.3.4 Rejected case(s) and cases not matched to controls

None of the 5 cases rejected because they did not conform with the case definition (3 cases of CNS demyelination, 1 case of polyarthritis and 1 case of autoimmune thyroiditis) (according to patients' interviews before reject and/or physicians' reports) had been vaccinated or had received a prescription for Cervarix® that could be documented on Cervarix® use.

Table 5. Rejected cases

Recuited as	Number of cases rejected	Rejected
CD/MS	3	2 cases with a vascular etiology 1 case of Behcet disease
CTD (Suspicion of rheumatoid arthritis)	1	1 case not confirmed afterwards (no sign of chronicity)
AIT	1	1 case of hyperemesis gravidarum with transient thyrotoxicosis

1 eligible definite case of T1D could not be matched with any controls. This case had not been vaccinated with Cervarix®.

1.3.5 Interview success rate in cases

Table 6 present the rate of success of interviews for all disorders combined. It also provides the rate of success for controls

Table 6. Rate of success

	Eligible patients recruited	Eligible patients interviewed*	Eligible patients Success rate
All cases of auto-immune disorders combined	569	511	90%
Eligible referents	2801	2209	79%

*or parents interviewed

The success rate of interview was similar in the total population of autoimmune disorders patients of all age and gender recruited in PGRx (2819/3131 or 90 %) and in the 11-25 year old females (or their parents) interviewed for the Cervarix-autoimmune disorders Study patients (90 %). Rates of success are provided for each disorder in Table 4 above.

Among the 58 autoimmune disease cases not documented on exposure:
- 14 (24%) refused to participate afterwards, at the moment of the interview.
- 44 (76%) could not be reached for the interview (after numerous attempts up to 90 days following recruitment.

For 19 (21%) of these 58 cases, we could obtain from their physician the information on the prescriptions these patients had in the 2 years prior to the index date. It was found that 4 (21%) had a reported HPV vaccine on the prescriptions and none of these documented prescriptions mentioned Cervarix®.

1.4 Recruitment of controls

1.4.1. Period of recruitment of referents

The period of recruitment of the pool of reference in PGRx started in early 2007. For this study, eligible referents recruited as controls were selected from the pool for the study started on April 2008 and ended on September 2014. These dates are in accordance with the matching of controls to cases.

1.4.2. Selection of controls

An average of 4 controls per case was sought.

Controls were selected amongst the 15723 patients of the PGRx reference pool available and recruited during the study period. Referents meeting all the inclusion criteria for the study and presenting with none of the exclusion criteria were selected, without consideration in a first instance for personal history of autoimmune disorder (N= 2209). They were then matched to cases, excluding in each instance those referents with a personal history of the autoimmune disorder from which the considered case was suffering.

For the combined analysis, a maximum of 10 controls per case was sought for in order to find as many controls as possible (average: 3.8, range 1-10).

1.4.3. Controls selected

Table 7 describes the distribution of the referents according to the inclusion and exclusion criteria for this study.

Table 7. Recruitment of referents and controls selected for the combined analysis of all studied AID

	PGRx pool of referents	Matched eligible controls 11-25 y.o. without personal history of the AID of their matched case and interviewed
Referents	15723	1953

The detailed distribution (flow charts) of referents (controls) at each stage of recruitment and matching is displayed below for all referents and controls used for all autoimmune disorders combined. The distribution of control sets for individual disorders are appended.

Referents with the history of AID of their matched control were dropped from the matching and could be matched to another case. The total number of matched controls was 1953 for the analysis of all AID combined.

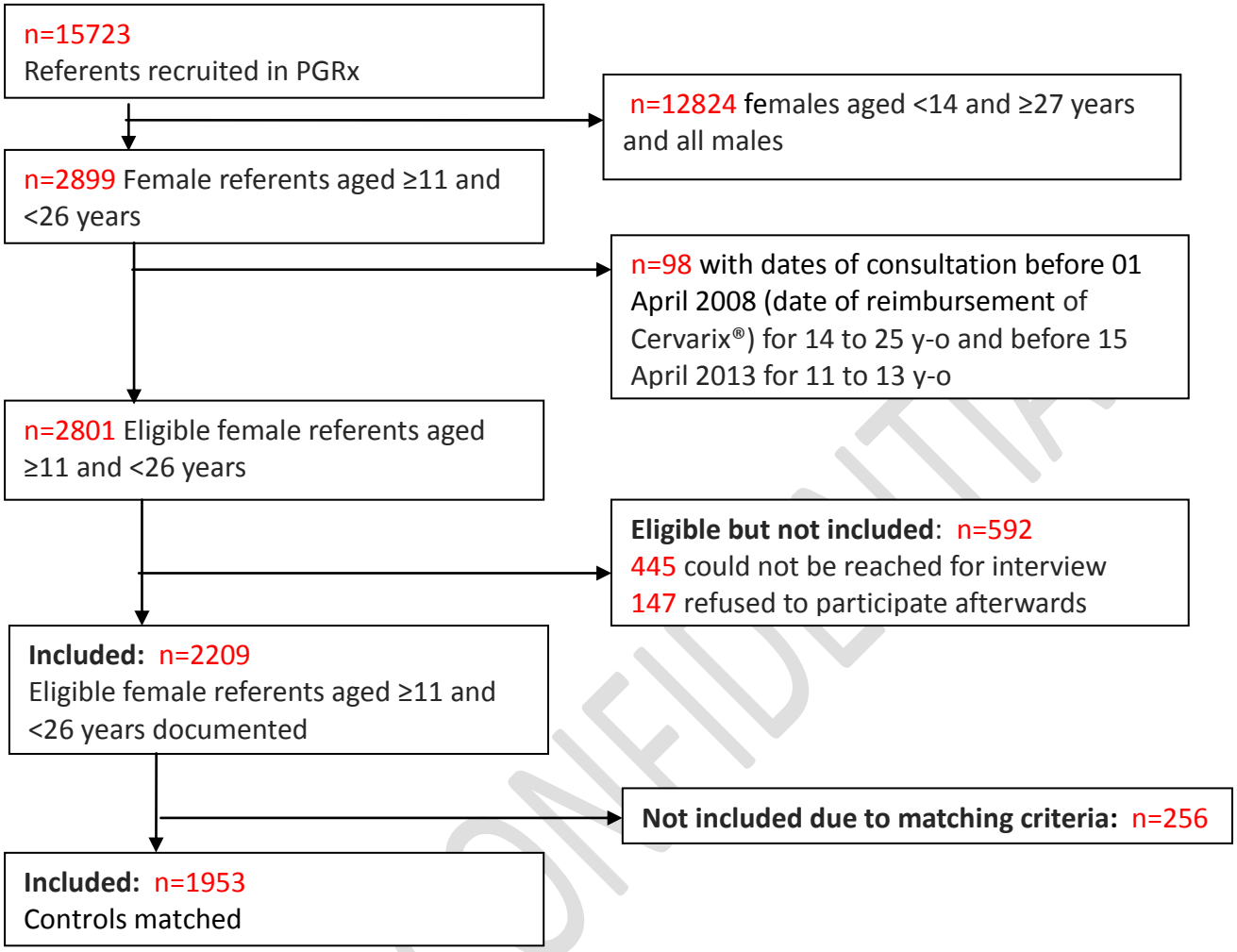
1.4.4. Interview success rate of referents

The average success rate in terms of proportion of interviewed patients for all PGRx referents was 86% (13595/15723). The success rate in the eligible referents for all autoimmune disorders combined in this study was 79% (2209/2801).

Among the 592 eligible referent-patients not interviewed:
- 147 (25%) refused to participate afterwards, at the moment of the interview.
- 445 (75%) could not be reached for the interview (after numerous attempts up to 90 days following recruitment).

For 525 (89%) of these 592 referents, we could obtain from their physician the information on the prescriptions these patients had in the 2 years prior to the index date. It was found that 78 (15%) had a reported HPV vaccine on the prescriptions and 11 (2%) reported Cervarix®.

Figure 4. Flow chart showing identification of controls for all studied autoimmune disorders combined within the pool of referents



2. Results of investigations and analysis for exposure validation

In this section, we present results of a series of studies performed to validate the quality of data. We have studied: 1- the quality of the sample of controls, 2- the vaccination coverage in the referents, 3- the validity of the interviews (a guided patients self reporting), 4 – detailed investigations on exposure ascertainment and 5- assessment of the agreement between the physicians reports through prescriptions and the patients self-report through the interviews.

2.1. Validity of referents and controls

2.1.1 Comparison between the pool of referents and the French general population in general practice

The distribution of reasons for the consultation in the referents recruited in PGRx, standardised by age and gender was compared to the survey of the Ministry of Health Statistical department (DREES) conducted in a representative sample of general practices in France.

The overall distributions of reasons of consultation were comparable (see Table 8 below).

Table 8. Comparison of reasons for the consultation of PGRx referents with the data from DREES study (after standardisation on age and gender structure of the French population)

	DREES Study n (%)*	**PGRx** n (%)*
Number of GPs centres n	922 [54432 after standardisation]	406
Reasons for the consultation		
Chronic pathology (follow-up visit)	42%	41%
Worsening of chronic pathology	7%	3%
Acute signs and symptoms	36%	41%
Other (administrative, counseling, preventive action, certificate)	9%	14%
None	N/C	0.5%

* Percentage (%) and class size (n) for categorical variables.

2.1.2 Coverage by HPV vaccine in the referents vs. coverage in external sources of information

Figure 5. Use of HPV vaccines in 11-25 y-o. females eligible referents by year of birth

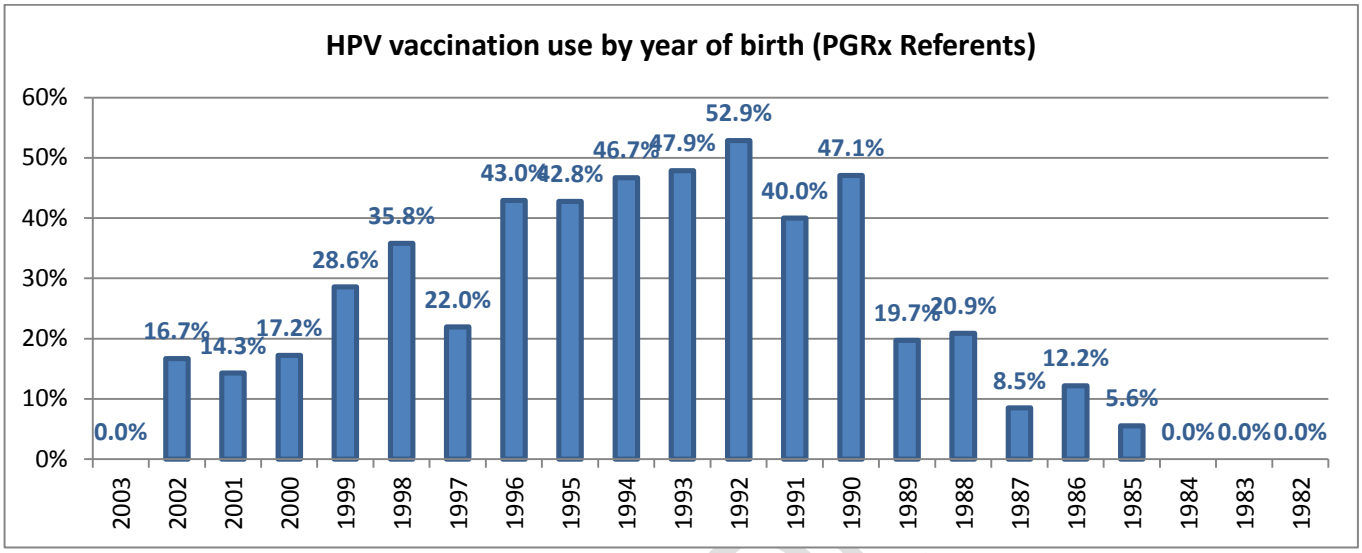
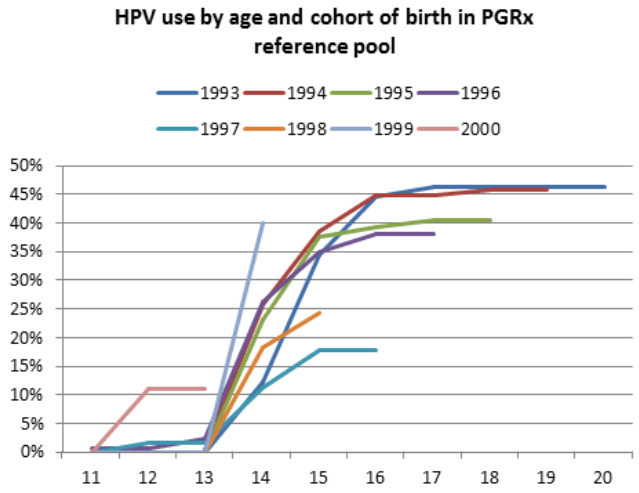
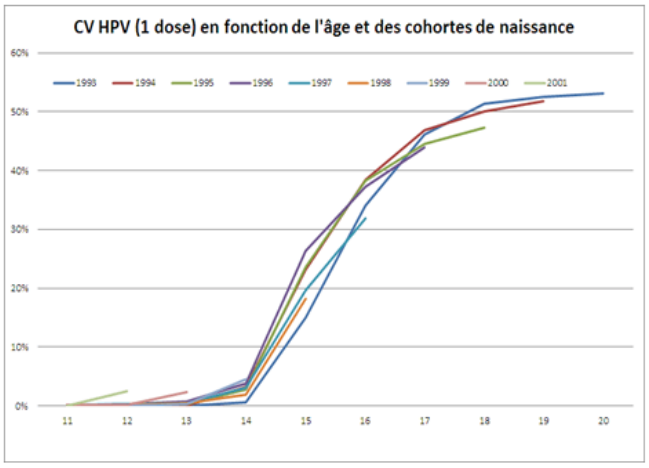


Figure 6. HPV Vaccination coverage (1 shot) by age and year of birth cohorts





Source:HCSP Rapport 10 juillet 2014

The dynamic of exposure by cohort of birth were close to HCSP data with systematically a 5% less vaccine reported for PGRx referents; one explanation given was that patients can buy the vaccine and finally do not get vaccined. The average exposure of referents is consistent with sales figures globally.

2.1.3 Coverage according to patients reports vs physician prescriptions

The estimates of coverage derived from patient reports during interviews vs those obtained from physician's prescriptions were calculated. The coverage was estimated:

a) in all eligible referents (female 11 – 25 y.o.) using interviews

b) in eligible referents for whom physician's records were available, using physician's record results.

Table 9 shows that both estimates of coverage were very similar

Table 9. Coverage according to 3 studies in PGRx

	All referents (f. 11 – 25 y.o.)	Referents with both interviews and physician's records
Source	Interviews	Physician's records
N	n=2209	n=2117
Estimate of HPV Vaccination in the 2 years (DI included)	27.0%	24.9%
Estimate of Cervarix® in the 2 years (DI included)	1.2%	1.5%

The objective of this evaluation was to measure the agreement between patient's self reports and physician prescriptions of HPV vaccine and Cervarix® as reported. The agreement was 98% for all HPV vaccine in the pool of referents.

2.2 Validity of the ascertainement of exposure to HPV vaccine

Among the 921 patients (cases and controls) who reported a HPV vaccine shot at any time, 872 (95%) (100/109 (92%) in cases and 772/812 (95%) in referents) had this vaccination confirmed objectively by one of the means described further above: batch number, copy of prescription, physician report, vaccination certificate.
Among the 36 patients (cases and controls) who reported a Cervarix® shot at any time, 36 (100 %) had this vaccination confirmed objectively.

Table 10. Rate of confirmation of HPV vaccine and Cervarix® use in case and controls

Vaccine	**Patients reporting vaccine use N**	**Success rate of objectivation %**
Referents		
HPV	812	95%
Cervarix	34	100%
AID Cases		
HPV	109	92%
Cervarix	2	100%

The confirmation of Cervarix® vaccination was complete.

2.3. Detailed investigations on exposure ascertainment

2.3.1 Investigations on exposure ascertainment in referents population

Table 11 shows the objectivation of HPV vaccine use in the 24 months before index date in referents. Among the 2209 referents, an objective confirmation of HPV vaccine use or non use was obtained for 2151 (97.4%) referents.
After investigations, the agreement for vaccine use between patient's self reports and physician's records, was 98,4% for referents with a PABAK*=0,97 (prevalence-adjusted bias-adjusted Kappa).

Table 11. Objectivation of HPV vaccine use in the 24 months before index date in referents

Referents n=2151 (97.4%) over 2209		**HPV vaccine use in physician's records in the 24 months before index date**	
		Yes	**No**
HPV vaccine use self-reported by the patient in the 24 months before index date	**Yes**	**577 (26.8%)** Counted as certain exposure	**19 (0.9%)** Counted as uncertain exposure
	No	Among the 129 patients initially Yes/No: -111 confirmed no use before index date. They became No/No and counted as not exposed. - 3 confirmed exposure before the 24 month time window. They became No/No and counted as uncertain exposure. **15 (0.7%)** remained as a disagreement between physician's reports and patients self reports. Counted as no exposure And as uncertain exposure in a sensitivity analysis	Initially1426, to which were added the 111+3 after investigation: **1540 (71.6%)** Counted as no exposure

2.3.2 Investigations on exposure ascertainment in cases population

Table 12 shows the objectivation of HPV vaccine use in the 24 months before index date in cases population. Among the 511 cases, an objective confirmation of HPV vaccine use or non use was obtained for 334 (65.4%) cases.
After investigations, the agreement for vaccine use between patient's self reports and physician's records was 99,7% for cases with a PABAK=0,99 (prevalence-adjusted bias-adjusted Kappa).

Table 12. Objectivation of HPV vaccine use in the 24 months before index date in cases population

Cases n=334 (65.4%) over 511		**HPV vaccine use in physician's records in the 24 months before index date**	
		Yes	**No**
HPV vaccine use self-reported by the patient in the 24 months before index date	**Yes**	**58 (17.4%)** Counted as certain exposure	**1 (0.3%)** Counted as uncertain exposure
	No	Among the 6 patients initially Yes/No: - 5 confirmed no use before index date. They became No/No and counted as not exposed. - 1 confirmed exposure before the 24 month time window. She became No/No and counted as uncertain exposure **0 (0%)** remained as a disagreement between physician's reports and patients self reports.	Initially 269, to which were added the 5+1 after investigation: **275 (82.3%)** Counted as no exposure

3. Results on the 'Surveillance Study'

The objective of the surveillance study was to monitor a large number of centres recruiting patients with incident autoimmune diseases in France and identify all cases of eligible AIDs observed in these centres after the reimbursement of Cervarix® on April 2008 and for more than 6 years thereafter.

The 382 initiated centres were contacted by CRAs and/or the project manager at least once a month to enforce and closely monitor the recruitment of cases, and particularly to ensure a consecutive recruitment of cases.
Among these 382 centres, 299 recruited at least one patient and 168 recruited at least one patient eligible for the study (female 11-25 y-o) with a date of AID first symptoms between April 2008 and September 2014.

The figure below shows the monthly distribution of cases according to their date of first symptoms.

Figure 7A. Eligible reported cases (n=574) recruitment according to date of first symptoms from April 2008 to March 2011

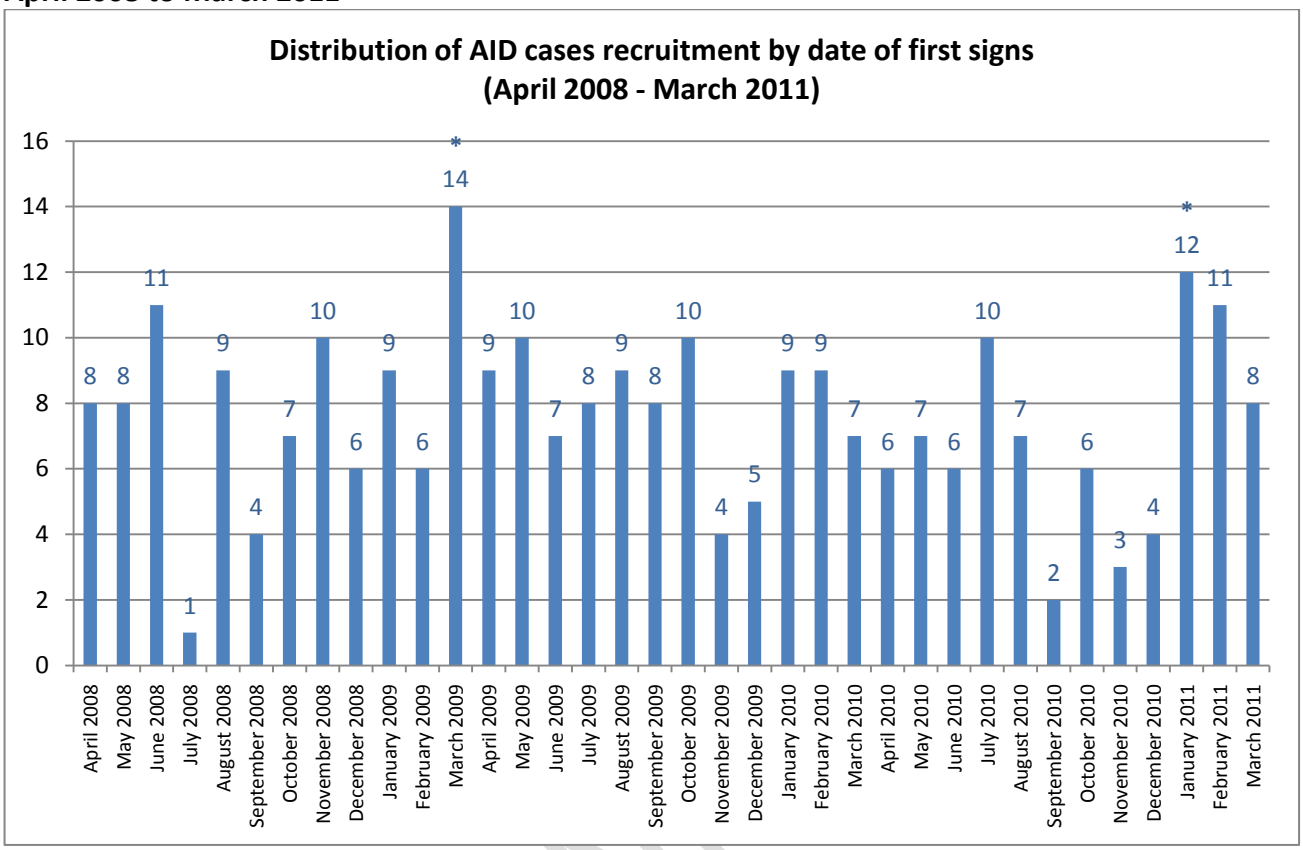
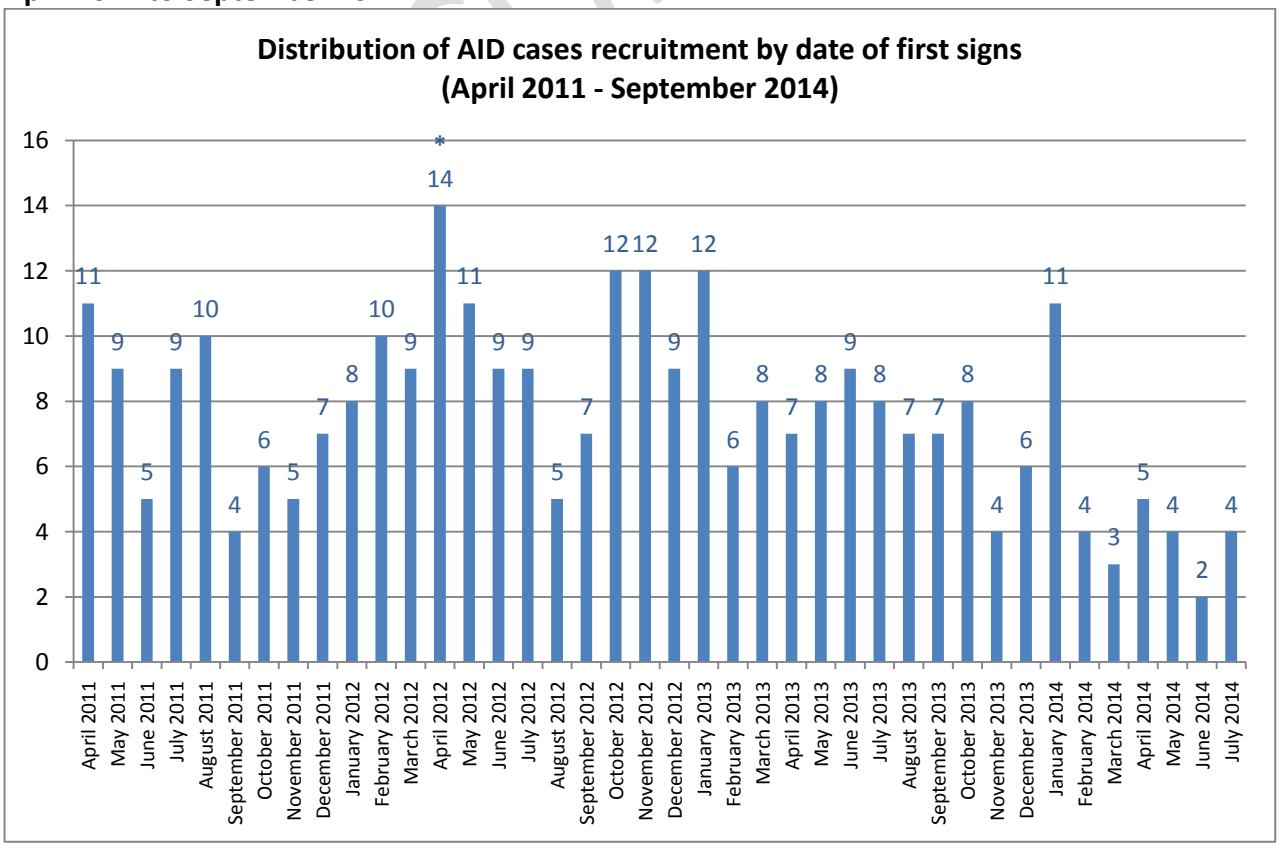


Figure 7B. Eligible reported cases (n=574) recruitment according to date of first symptoms from April 2011 to September 2014



The recruitment per year of index date is:

- **April-Dec 2008**: 64 (9 months)
- **2009**: 99
- **2010:** 76
- **2011**: 97
- **2012**: 115
- **2013**: 90
- **Jan-Sept 2014**: 33

The table below provides the results of the continuous monitoring of cases. Each month, the number of events occurred were compared to the intensity of events over the 3 preceding months using a Poisson model (Model 1). When the difference was statistically significant, the number of HPV vaccine users during the month of interest was examined (in bold and with * in the table).
The table below also shows the results from the second method which used as a reference the cumulative number of events during the months preceding the observed month (Model 1). Similarly as the preceding method, when the difference was statistically significant the number of HPV vaccine users during the month of interest was looked at (in bold and with * in the table).

Table 13: Results of the first and the second model applied for the surveillance study.

Observed month	Nb of cases occured in the observed month	Intensity of events over the 3 preceding months P MODEL 1	Intensity of events over the preceding month (cumulative) P MODEL 2
April 2008	8	.	.
May 2008	8	.	.
June 2008	11	.	.
July 2008	**1**	**0.031***	**0.031***
August 2008	9	0.4547	0.5119
September 2008	4	0.305	0.2425
October 2008	7	0.3811	0.953
November 2008	10	0.2951	0.2777
December 2008	6	0.7391	0.659
January 2009	9	0.6834	0.5082
February 2009	6	0.4699	0.6442
March 2009	**14**	**0.0445***	**0.0213***
April 2009	9	0.8514	0.6684
May 2009	10	0.9263	0.4642
June 2009	7	0.2774	0.7318
July 2009	8	0.8431	0.9817
August 2009	9	0.8431	0.7157
September 2009	8	1	1
October 2009	10	0.6261	0.495
November 2009	4	0.1301	0.1632
December 2009	5	0.4395	0.3139
January 2010	9	0.3852	0.6656

Observed month	Nb of cases occured in the observed month	Intensity of events over the 3 preceding months P MODEL 1	Intensity of events over the preceding month (cumulative) P MODEL 2
February 2010	9	0.3206	0.6806
March 2010	7	0.8331	0.7611
April 2010	6	0.4699	0.5203
May 2010	7	0.9146	0.7888
June 2010	6	0.8209	0.5407
July 2010	10	0.2423	0.4119
August 2010	7	0.8331	0.791
September 2010	2	0.0683	0.0571
October 2010	6	0.9081	0.5822
November 2010	3	0.4193	0.1157
December 2010	4	0.8815	0.2282
January 2011	**12**	**0.0109***	**0.0878**
February 2011	11	0.1451	0.1955
March 2011	8	0.7698	0.8531
April 2011	11	0.8586	0.2131
May 2011	9	0.7816	0.6161
June 2011	5	0.1986	0.3485
July 2011	9	0.8431	0.6075
August 2011	10	0.483	0.3932
September 2011	4	0.1993	0.1968
October 2011	6	0.5928	0.5724
November 2011	5	0.565	0.3628
December 2011	7	0.4623	0.8629
January 2012	8	0.4984	0.8471
February 2012	10	0.2951	0.365
March 2012	9	0.8431	0.5978
April 2012	**14**	**0.1797**	**0.0238***
May 2012	11	1	0.2425
June 2012	9	0.5386	0.6602
July 2012	9	0.5386	0.6668
August 2012	5	0.1734	0.3219
September 2012	7	0.8331	0.7882
October 2012	12	0.1364	0.1343
November 2012	12	0.2515	0.1432
December 2012	9	0.7152	0.6966
January 2013	12	0.7963	0.1545
February 2013	6	0.172	0.4871
March 2013	8	0.7698	0.9857
April 2013	7	0.616	0.7382
May 2013	8	0.7479	0.9816
June 2013	9	0.6834	0.7082

Observed month	Nb of cases occured in the observed month	Intensity of events over the 3 preceding months P MODEL 1	Intensity of events over the preceding month (cumulative) P MODEL 2
July 2013	8	1	0.9866
August 2013	7	0.6835	0.7373
September 2013	7	0.7559	0.7409
October 2013	8	0.8331	0.9787
November 2013	4	0.2648	0.1731
December 2013	6	0.9081	0.5092
January 2014	11	0.1132	0.2663
February 2014	4	0.305	0.1762
March 2014	3	0.1698	0.0974
April 2014	5	0.7184	0.3273
May 2014	4	1	0.1895
June 2014	2	0.3641	0.0576
July 2014	4	0.8815	0.2008

* $p<0.05$

Model 1: 2 peaks (March 2009 and January 2011) were significantly higher than the average occurrences over the 3 preceding months.

- Two patients reported an HPV vaccination out of the 14 in March 2009 and 12 in January 2011 AID cases. None was Cervarix® use.

Model 2 : 2 peaks (March 2009 and April 2012) were significantly higher than the occurrences over the cumulative preceding months.

- Two patients in March 2009 and one patient in April 2012 reported an HPV vaccination out of the 14 AID cases that occurred in each of these months. None was Cervarix® use

In all, both methods concurred to identify significant variations over time in the number of cases of AID occurring over more than 6 years of surveillance. None of the peaks was attributable to HPV vaccine or Cervarix® use.

4. Description of Risk factors

4.1 General risk factors

The general risk factors of cases and matched controls included in the combined analysis are described in Table 14 below.

Alcohol and tabacco consumption showed no significant association with incidence of autoimmune in the studied population with respectively 91.8% of cases and 93.0% of referents who occasionnaly or never drink alcohol; 67.1% of cases vs 64.6% of referents who never smoked.

Geographical origin and first degree familial history or personal history of autoimmune disorder was associated with an elevated odds ratio for the incident autoimmune diseases studied with respectively an adjusted OR: 3.68 [95%CI: 2.76 - 4.89] for patients with both parents from

Southern Europe or Africa or others countries; and adjusted OR: 1.86 [95%CI: 1.33 - 2.60] for patients reporting a AID in first degree relatives.
The use of oestroprogestative/contraceptive before index date is associated with a decreased odds ratio for the incident autoimmune diseases with an adjusted OR: 0.64 [95%CI: 0.50 - 0.83].

Table 14. Description of general risk factors and adjusted odds ratio for the occurrence of cases of autoimmune diseases

VARIABLES	CASES	CONTROLS*	Matched Adjusted ** OR 95% CI
MATCHING CRITERIA			
Age (matching)	**n=510**	**n=1953**	
Mean [standard deviation]	20.1 [3.7]	19.9 [3.6]	NA
Median [Min-Max]	20.5 [11.5 - 26.0]		
Region of residence	**n=510**	**n=1953**	
North	273 (53.5%)	51.4%	NA
South	237 (46.5%)	48.6%	
SOCIO DEMOGRAPHICS			
Social status	**n=510**	**n=1953**	
Lives with at least one person	454 (89.0%)	88.8%	NC
Lives alone	56 (11.0%)	11.2%	
Main occupation	**n=510**	**n=1953**	
Employed	160 (31.4%)	28.5%	NC
Unemployed	57 (11.2%)	9.8%	
Students	293 (57.5%)	61.7%	
RISK FACTORS			
Smoking	**n=510**	**n=1953**	
Smoker	141 (28.0%)	32.0%	0.95 [0.73 - 1.23]
Former smoker (has stopped smoking for >= 1 year)	25 (5.0%)	3.5%	1.75 [1.02 - 3.02]
Never smoked	338 (67.1%)	64.6%	1
Missing / Choose not to answer	6		
Alcohol consumption (in a normal week before index date)	**n=510**	**n=1953**	
Daily or almost daily	1 (0.2%)	0.3%	0.58 [0.06 - 5.97]
A few times per week	40 (8.0%)	6.7%	1.52 [0.98 - 2.37]
Occasionally or never	462 (91.8%)	93.0%	1
Missing / Choose not to answer	7		
Geographical origin£	**n=510**	**n=1953**	
Northern Europe or North America	289 (56.7%)	76.8%	1
Southern Europe or Africa or others	141 (27.6%)	9.0%	3.68 [2.76 - 4.89]
Mixed or Missing	80 (15.7%)	14.2%	1.61 [1.18 - 2.19]
Personal or familial history of AID :	**n=510**	**n=1953**	
Yes	75 (14.7%)	8.6%	1.86 [1.33 - 2.60]
No	397 (77.8%)	79.2%	1
Don't know / Missing	38 (7.5%)	12.3%	0.49 [0.30 - 0.78]
Vaccines received except HPV in the 2 years before index date$	**n=510**	**n=1953**	
Yes	134 (26.3%)	26.8%	1.03 [0.80 - 1.31]
Without date / Index Date	33 (6.5%)	6.1%	1.02 [0.66 - 1.58]
No	343 (67.3%)	67.2%	1

VARIABLES	CASES	CONTROLS*	Matched Adjusted ** OR 95% CI
Any use of estroprogestatives/contraceptives before index date	**n=510**	**n=1953**	
Yes	238 (46.7%)	58.0%	0.64 [0.50 - 0.83]
No	272 (53.3%)	42.0%	1

*Proportions weighted by the number of matched controls per cases
£ Regions of birth of the patient's parents (father and mother)
$ one or more vaccine shots against the same infection
** Conditional logistic regression adjusted for f/phaid, geographical origin, smoking, alcohol, any use of estroprogestatives/contraceptives before index date, vaccines received except HPV in the 2 years before index date

Season of first signs occurrence in cases was evenly distributed (Table 15).

Table 15. Season of occurrence of first symptoms in cases

Season of first symptoms of cases n=511	
Spring	145 (28.4%)
Summer	129 (25.3%)
Autumn	106 (20.8%)
Winter	130 (25.5%)

4.2 Studies of potential sources of confounding

In order to identify potential confounders, risk factors were assessed for associations with HPV vaccination vaccination.

4.2.1 Propensity to be vaccinated according to the risk factors

Table 16 presents the results of a multivariate unconditional logistic regression applied to all eligible documented referents (n=2209) in order to assess the adjusted odds ratio for the use of HPV vaccine (before index date) according to the presence or absence of the risk factors listed (all factors are introduced in the model).

Table 16. Propensity to be vaccinated according to the risk factors

VARIABLES	USER n (%)	NON USER n (%)	Adjusted OR 95% CI
RISK FACTORS			
Smoking	**n=810**	**n=1399**	
Smoker / Former smoker (has stopped smoking for >= 1 year)	214 (26.4%)	423 (30.2%)	0.83 [0.67 - 1.02]
Never smoked	596 (73.6%)	976 (69.8%)	1
Alcohol consumption (in a normal week before index date)	**n=810**	**n=1399**	
Daily or almost daily / A few times per week	35 (4.3%)	71 (5.1%)	1.12 [0.71 - 1.75]
Occasionally or never	775 (95.7%)	1328 (94.9%)	1
Personal or familial history of AID :	**n=810**	**n=1399**	
Yes	61 (7.5%)	94 (6.7%)	1.18 [0.83 - 1.68]
No	654 (80.7%)	1106 (79.1%)	1
Don't know / Missing	95 (11.7%)	199 (14.2%)	0.75 [0.57 - 0.98]
Geographical origin£	**n=810**	**n=1399**	
Northern Europe or North America	669 (82.6%)	1055 (75.4%)	1
Southern Europe or Africa or others	43 (5.3%)	148 (10.6%)	0.53 [0.36 - 0.76]
Mixed or Missing	98 (12.1%)	196 (14.0%)	0.88 [0.67 - 1.15]
Vaccines received except HPV in the 2 years before index date	**n=810**	**n=1399**	
Yes (incl. Without date / Index date)	330 (40.7%)	468 (33.5%)	1.32 [1.09 - 1.59]
No	480 (59.3%)	931 (66.5%)	1
Any use of estroprogestatives/contraceptives before index date	**n=810**	**n=1399**	
Yes	402 (49.6%)	609 (43.5%)	1.73 [1.39 - 2.14]
No	408 (50.4%)	790 (56.5%)	1

£ Regions of birth of the patient's parents (father and mother)
$ one or more vaccine shots against the same infection
** Unonditional logistic regression adjusted for age, region of residence, f/phaid, geographical origin, smoking, alcohol, any use of estroprogestatives/contraceptives before index date, vaccines received except HPV in the 2 years before index date

The study showed that alcohol consumption and smoking did not significantly affect the propensity to be vaccinated by HPV vaccine. Vaccination was more frequent in patients who had received another vaccine in the two years before the index date. Those who used an oral

contraceptive were more likely to be vaccinated by HPV vaccine (it is not always known with precision which came first). Patients with a geographical origin from Southern Europe or Africa were less likely to have been vaccinated with HPV vaccine.

4.2.2. HPV vaccine use according to history of autoimmune diseases

First degree familial or personal history of autoimmune diseases was further explored as a potential confounder. Vaccination in controls with or without a personal or familial history of autoimmune diseases, or with such a history unknown or missing, was described for referents of all autoimmune diseases combined (Table 16). In the propensity analysis conducted in the referents, the adjusted odds ratio for being vaccinated by HPV vaccine in presence of familial or personal history of AID was 1.18 (95% CI [0.83 - 1.68]).

Nevertheless, the familial or personnal history of autoimmune disease was explored as counfounder in stratified analysis.

5. Results on the 'Risk study'

5.1 General description of HPV and Cervarix® exposure

5.1.1. Detailed categories of HPV vaccine and Cervarix® exposure in definite and possible cases and their matched controls

Table 17 displays detailed categories of HPV vaccine and Cervarix® exposure in definite and possible cases and their matched controls, according to the definitions provided section 8.3.2 and to a new categorisation of these definitions provided in the table.

Table 17. Detailed categories of HPV vaccine and Cervarix® exposure in definite and possible cases and their matched controls

Exposure	DEFINITE AND POSSIBLE CASES n (%)	CONTROLS n (%)
EXPOSURE PRIMARY TIME-WINDOW		
HPV vaccines	**n=510**	**n=1953**
Confirmed	52 (10.2%)	401 (20.5%)
Unconfirmed	1 (0.2%)	6 (0.3%)
Without Date	5 (1.0%)	15 (0.8%)
Index date	0 (0.0%)	26 (1.3%)
Past	47 (9.2%)	247 (12.6%)
Not exposed	405 (79.4%)	1258 (64.4%)
Cervarix	**n=510**	**n=1953**
Confirmed	2 (0.4%)	18 (0.9%)
Unconfirmed	0 (0.0%)	0 (0.0%)
Without Date	0 (0.0%)	0 (0.0%)
Index date	0 (0.0%)	3 (0.2%)
Past	0 (0.0%)	10 (0.5%)
Not exposed	508 (99.6%)	1922 (98.4%)
Exposure primary time-window: **i. At risk time-window: Confirmed + Unconfirmed + on index date** **ii. Past time-window: Past (confirmed and unconfirmed) + Without date** **iii. Not exposed**		
HPV vaccines	**n=510**	**n=1953**
At risk time-window	53 (10.4%)	433 (22.2%)
Past time-window	52 (10.2%)	262 (13.4%)
Not Exposed	405 (79.4%)	1258 (64.4%)
Cervarix	**n=510**	**n=1953**
At risk time-window	2 (0.4%)	21 (1.1%)
Past time-window	0 (0.0%)	10 (0.5%)
Not Exposed	508 (99.6%)	1922 (98.4%)

5.1.2. Detailed categories and definition of HPV vaccine and Cervarix® exposure in definite cases and their matched controls

Table 18 displays detailed categories of HPV vaccine and Cervarix® exposure in definite cases and their matched controls, according to the definitions provided section 8.3.2, and to a new categorisation of these definitions provided in the table.

Table 18. Detailed categories and definition of HPV vaccine and Cervarix® exposure in definite cases and their matched controls

Exposure	DEFINITE CASES n (%)	CONTROLS n (%)
EXPOSURE PRIMARY TIME-WINDOW		
HPV vaccines	**n=478**	**n=1869**
Confirmed	51 (10.7%)	390 (20.9%)
Unconfirmed	1 (0.2%)	5 (0.3%)
Without Date	5 (1.0%)	14 (0.7%)
Index date	0 (0.0%)	26 (1.4%)
Past	45 (9.4%)	240 (12.8%)
Not exposed	376 (78.7%)	1194 (63.9%)
Cervarix	**n=478**	**n=1869**
Confirmed	2 (0.4%)	17 (0.9%)
Unconfirmed	0 (0.0%)	0 (0.0%)
Without Date	0 (0.0%)	0 (0.0%)
Index date	0 (0.0%)	3 (0.2%)
Past	0 (0.0%)	10 (0.5%)
Not exposed	476 (99.6%)	1839 (98.4%)
Exposure primary time-window: **i. At risk time-window: Confirmed + Unconfirmed + on index date** **ii. Past time-window: Past (confirmed and unconfirmed) + Without date** **iii. Not exposed**		
HPV vaccines	**n=478**	**n=1869**
At risk time-window	52 (10.9%)	421 (22.5%)
Past time-window	50 (10.5%)	254 (13.6%)
Not Exposed	376 (78.7%)	1194 (63.9%)
Cervarix	**n=478**	**n=1869**
At risk time-window	2 (0.4%)	20 (1.1%)
Past time-window	0 (0.0%)	10 (0.5%)
Not Exposed	476 (99.6%)	1839 (98.4%)

The exposure to HPV vaccine and Cervarix® is comparable between possible and definite vs. definite cases only, with 10.4% vs 10.9% within the at risk time-window, 10.2% vs 10.5% in the past time-window and 79.4% vs 78.7% not exposed, respectively.

5.1.3. Detailed categories of HPV vaccine and Cervarix® exposure in definite cases: final classification of cases vs. applied clinical algorithm

No difference was observed in term of exposure to HPV vaccine and Cervarix® exposure between cases classified as definite within the final case ascertainment process compared to cases classified as definite using only the case definition (cases definitions are appended).

Table 19. Detailed categories of HPV vaccine and Cervarix® exposure in definite cases: final classification of cases vs. applied clinical algorithm

Exposure	DEFINITE CASES: FINAL CLASSIFICATION n (%)	DEFINITE CASES: CLINICAL ALGORITHM n (%)
EXPOSURE PRIMARY TIME WINDOW		
HPV vaccines	**n=478**	**n=324**
Confirmed	51 (10.7%)	33 (10.2%)
Unconfirmed	1 (0.2%)	0 (0.0%)
Without Date	5 (1.0%)	4 (1.2%)
Index date	0 (0.0%)	0 (0.0%)
Past	45 (9.4%)	28 (8.6%)
Not exposed	376 (78.7%)	259 (79.9%)
Cervarix	**n=478**	**n=324**
Confirmed	2 (0.4%)	1 (0.3%)
Unconfirmed	0 (0.0%)	0 (0.0%)
Without Date	0 (0.0%)	0 (0.0%)
Index date	0 (0.0%)	0 (0.0%)
Past	0 (0.0%)	0 (0.0%)
Not exposed	476 (99.6%)	323 (99.7%)

5.2 General analysis

5.2.1. General analysis for HPV vaccine use

Table 20A presents the distribution of HPV use before index date in all cases definite and possible, first individually for AID and All AID combined and their controls and the corresponding crude and adjusted odds ratios. The latter were adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date and vaccines other than HPV received within two years before the index date

In the General analysis, using the definite and possible cases (n= 510) which could be matched to controls (n=1953) and considering any use of HPV vaccine before index date, the adjusted odds ratio was 0.64 (95% CI 0.49, 0.83).

Table 20A. Any use of HPV vaccine before index date for definite and possible cases of AID (individually and all combined) and their matched controls and corresponding odds ratios

Exposure	Cases n (%)	Controls n (%)	Matched Crude* OR 95% CI	Matched Adjusted** OR 95% CI
Any use before index date – DEFINITE & POSSIBLE CASES				
HPV vaccines				
CD/MS (116/893)	22 (19.0%)	282 (31.6%)	0.55 [0.32 - 0.94]	0.64 [0.37 - 1.12]
CTD (105/872)	23 (21.9%)	260 (29.8%)	0.69 [0.41 - 1.18]	0.82 [0.46 - 1.46]
GBS (13/130)	1 (7.7%)	28 (21.5%)	0.28 [0.03 - 2.32]	NC
T1D (93/870)	17 (18.3%)	259 (29.8%)	0.50 [0.28 - 0.89]	0.54 [0.30 - 0.98]
AIT (106/876)	22 (20.8%)	277 (31.6%)	0.56 [0.33 - 0.95]	0.66 [0.38 - 1.15]
ITP (77/698)	20 (26.0%)	195 (27.9%)	0.95 [0.54 - 1.66]	0.97 [0.54 - 1.72]
ALL (510/1953)	**105 (20.6%)**	**695 (35.6%)**	**0.59 [0.46 - 0.76]**	**0.64 [0.49 - 0.83]**

CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura ; ALL : All AID combined.

* Conditional logistic regression using exposure status

**: Conditional logistic regression on matched case-control sets adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date, number of vaccines other than HPV received within two years before the index date

5.2.2. General analysis for Cervarix® use

Table 20B presents the distribution of Cervarix® use before index date in all cases definite and possible, first individually for AID and All AID combined and their controls and the corresponding crude odds ratios. The small numbers did not allow estimating adjusted ORs.

In the General analysis, using the definite and possible cases (n= 510) which could be matched to controls (n-1953) and considering any use of Cervarix® before index date, the crude odds ratio was 0.30 (95% CI 0.07, 1.27).

Table 20B. Any use of Cervarix® before index date for definite and possible cases of AID (individually and all combined) and their matched controls and corresponding odds ratios

Exposure	Cases n (%)	Controls n (%)	Matched Crude* OR 95% CI	Matched Adjusted** OR 95% CI
Any use before index date – DEFINITE & POSSIBLE CASES				
Cervarix				
CD/MS (116/893)	0 (0.0%)	4 (0.4%)	NC	NC
CTD (105/872)	2 (1.9%)	5 (0.6%)	NC	NC
GBS (13/130)	0 (0.0%)	1 (0.8%)	NC	NC
T1D (93/870)	0 (0.0%)	12 (1.4%)	NC	NC
AIT (106/876)	0 (0.0%)	9 (1.0%)	NC	NC
ITP (77/698)	0 (0.0%)	12 (1.7%)	NC	NC
ALL (510/1953)	**2 (0.4%)**	**31 (1.6%)**	**0.30 [0.07 - 1.27]**	**NC**

CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura ; ALL : All AID combined.
* Conditional logistic regression using exposure status
**: Conditional logistic regression on matched case-control sets adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date, number of vaccines other than HPV received within two years before the index date

5.3 Main analysis

5.3.1. Main analysis for HPV vaccine exposure (as defined per protocol)

Table 21A presents the distribution of HPV exposure in the primary time-window for each disease in definite cases, first individually for AID and All AIDs combined (mixed time-window) and their controls and the corresponding crude and adjusted odds ratios. The latter were adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date and vaccines other than HPV received within two years before the index date

In the Main analysis, using all definite cases (n= 478) which could be matched to controls (n-1869) and considering HPV vaccine exposure in the primary time-windows at risk, the adjusted odds ratio was 0.58 (95% CI 0.41, 0.83).

Table 21A. HPV vaccine exposure (at risk TW/past TW/Not exposed) in the primary time-window at risk for definite cases of AID (individually and all combined) and their matched controls and corresponding odds ratios

Exposure	Cases n (%)	Controls n (%)	Matched Crude* OR 95% CI	Matched Adjusted** OR 95% CI
At risk time-window – DEFINITE CASES				
HPV vaccines				
CD/MS (113/863)	7 (6.2%)	173 (20.0%)	0.28 [0.12 - 0.64]	0.31 [0.13 - 0.73]
CTD (92/769)	14 (15.2%)	147 (19.1%)	0.78 [0.40 - 1.52]	0.84 [0.41 - 1.73]
GBS (13/130)	0 (0.0%)	2 (1.5%)	-	-
T1D (86/804)	14 (16.3%)	189 (23.5%)	0.56 [0.30 - 1.06]	0.61 [0.32 - 1.17]
AIT (97/802)	6 (6.2%)	126 (15.7%)	0.28 [0.11 - 0.74]	0.35 [0.13 - 0.92]
ITP (77/698)	11 (14.3%)	87 (12.5%)	1.18 [0.58 - 2.42]	1.17 [0.56 - 2.41]
ALL (478/1869)	**52 (10.9%)**	**421 (22.5%)**	**0.54 [0.38 - 0.75]**	**0.58 [0.41 - 0.83]**

CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura ; ALL : All AID combined.
* Conditional logistic regression using exposure status
**: Conditional logistic regression on matched case-control sets adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date, number of vaccines other than HPV received within two years before the index date

5.3.2. Main analysis for Cervarix® exposure (as defined per protocol)

Table 21B presents the distribution of Cervarix® in the primary time-window for each disease in definite cases, first individually for AID and All AID combined (mixed time-window) and their

controls and the corresponding crude odds ratios. The small numbers did not allow estimating adjusted ORs.

In the Main analysis, using all definite cases (n= 478) which could be matched to controls (n-1869) and considering Cervarix® exposure in the primary time-windows at risk, the crude odds ratio was 0.50 (95% CI 0.12, 2.19).

Table 21B. Cervarix® exposure (at risk time-window/past time-window /Not exposed) in the primary time-window at risk for definite cases of AID (individually and all combined) and their matched controls and corresponding odds ratios

Exposure	Cases n (%)	Controls n (%)	Matched Crude* OR 95% CI	Matched Adjusted** OR 95% CI
At risk time-window – DEFINITE CASES				
Cervarix®				
CD/MS (113/863)	0 (0.0%)	1 (0.1%)	NC	NC
CTD (92/769)	2 (2.2%)	4 (0.5%)	NC	NC
GBS (13/130)	0 (0.0%)	0 (0.0%)	NC	NC
T1D (86/804)	0 (0.0%)	11 (1.4%)	NC	NC
AIT (97/802)	0 (0.0%)	6 (0.7%)	NC	NC
ITP (77/698)	0 (0.0%)	3 (0.4%)	NC	NC
ALL (478/1869)	**2 (0.4%)**	**20 (1.1%)**	**0.50 [0.12 - 2.19]**	**NC**

CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura ; ALL : All AID combined.
* Conditional logistic regression using exposure status
**: Conditional logistic regression on matched case-control sets adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date, number of vaccines other than HPV received within two years before the index date

5.3 Secondary analyses

5.3.1. Secondary analysis for HPV vaccine exposure

Table 22 presents the distribution of HPV exposure in the primary time-window for each disease in definite and possible cases, first individually for AID and All AID combined (mixed time-window) and their controls and the corresponding crude and adjusted odds ratios. The latter were adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date and vaccines other than HPV received within two years before the index date

In the sceondary analysis, using the all definite and possible cases (n= 510) which could be matched to controls (n-1953) and considering HPV vaccine exposure in the primary time-windows at risk, the adjusted odds ratio was 0.56 (95% CI 0.40, 0.80).

Table 22. HPV vaccine exposure (at risk TW/past TW/Not exposed) in the primary time-window at risk for definite and possible cases of AID (individually and all combined) and their matched controls and corresponding odds ratios

Exposure	Cases n (%)	Controls n (%)	Matched Crude* OR 95% CI	Matched Adjusted** OR 95% CI
At risk time-window – DEFINITE AND POSSIBLE CASES				
HPV vaccines				
CD/MS (116/893)	7 (6.0%)	182 (20.4%)	0.26 [0.11 - 0.60]	0.29 [0.12 - 0.67]
CTD (105/872)	15 (14.3%)	166 (19.0%)	0.70 [0.37 - 1.32]	0.83 [0.42 - 1.66]
GBS (13/130)	0 (0.0%)	2 (1.5%)	NC	NC
T1D (93/870)	14 (15.1%)	194 (22.3%)	0.56 [0.30 - 1.05]	0.61 [0.32 - 1.16]
AIT (106/876)	6 (5.7%)	137 (15.6%)	0.26 [0.10 - 0.67]	0.31 [0.12 - 0.82]
ITP (77/698)	11 (14.3%)	87 (12.5%)	1.18 [0.58 - 2.42]	1.17 [0.56 - 2.41]
ALL (510/1953)	**53 (10.4%)**	**433 (22.2%)**	**0.52 [0.38 - 0.73]**	**0.56 [0.40 - 0.80]**

CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura ; ALL : All AID combined.

* Conditional logistic regression using exposure status

**: Conditional logistic regression on matched case-control sets adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date, number of vaccines other than HPV received within two years before the index date

5.3.2. Stratified analysis on geographical origin and f/phaid for any use of HPV vaccine

Table 23 presents the general analysis, stratified by geographical origin and history of autoimmune disorders in the first degree family and/or personal history of these diseases.

Table 23. Stratified analysis

Exposure	Cases n (%)	Controls n (%)	Unmatched Adjusted** OR 95% CI
Any use before index date – DEFINITE & POSSIBLE CASES			
HPV vaccines			
CD/MS (116/893)			
f/phaid+ / Northern (12/57)	2 (16.7%)	19 (33.3%)	0.54 [0.10 - 3.04]
f/phaid+ / Southern (5/19)	1 (20.0%)	4 (21.1%)	NC
f/phaid- / Northern (52/611)	13 (25.0%)	211 (34.5%)	0.69 [0.35 - 1.35]
f/phaid- / Southern (47/206)	6 (12.8%)	48 (23.3%)	0.54 [0.21 - 1.42]
CTD (105/872)			
f/phaid+ / Northern (7/48)	1 (14.3%)	13 (27.1%)	0.42 [0.04 - 3.92]
f/phaid+ / Southern (13/19)	5 (38.5%)	6 (31.6%)	0.86 [0.16 - 4.56]
f/phaid- / Northern (34/621)	5 (14.7%)	211 (34.0%)	0.43 [0.16 - 1.16]
f/phaid- / Southern (51/184)	12 (23.5%)	30 (16.3%)	1.40 [0.64 - 3.07]

GBS (13/130)			
f/phaid+ / Northern (0/8)	NA	NA	NA
f/phaid+ / Southern (0/2)	NA	NA	NA
f/phaid- / Northern (9/86)	1 (11.1%)	22 (25.6%)	0.33 [0.04 - 3.11]
f/phaid- / Southern (4/34)	0 (0.0%)	4 (11.8%)	NC
T1D (93/870)			
f/phaid+ / Northern (6/56)	1 (16.7%)	15 (26.8%)	0.72 [0.07 - 7.15]
f/phaid+ / Southern (3/15)	1 (33.3%)	6 (40.0%)	NC
f/phaid- / Northern (50/630)	11 (22.0%)	203 (32.2%)	0.57 [0.29 - 1.14]
f/phaid- / Southern (34/169)	4 (11.8%)	35 (20.7%)	0.51 [0.17 - 1.55]
AIT (106/876)			
f/phaid+ / Northern (16/56)	2 (12.5%)	19 (33.9%)	0.22 [0.04 - 1.11]
f/phaid+ / Southern (9/19)	1 (11.1%)	3 (15.8%)	NC
f/phaid- / Northern (54/607)	15 (27.8%)	218 (35.9%)	0.71 [0.38 - 1.32]
f/phaid- / Southern (27/194)	4 (14.8%)	37 (19.1%)	0.83 [0.26 - 2.59]
ITP (77/698)			
f/phaid+ / Northern (3/34)	0 (0.0%)	11 (32.4%)	NC
f/phaid+ / Southern (1/16)	0 (0.0%)	3 (18.8%)	NC
f/phaid- / Northern (46/493)	12 (26.1%)	155 (31.4%)	0.77 [0.38 - 1.55]
f/phaid- / Southern (27/155)	8 (29.6%)	26 (16.8%)	2.37 [0.91 - 6.18]
ALL (510/1953)			
f/phaid+ / Northern (44/107)	6 (13.6%)	40 (37.4%)	0.29 [0.11 - 0.77]
f/phaid+ / Southern (31/34)	8 (25.8%)	12 (35.3%)	0.66 [0.22 - 1.97]
f/phaid- / Northern (245/1420)	57 (23.3%)	532 (37.5%)	0.55 [0.40 - 0.76]
f/phaid- / Southern (190/392)	34 (17.9%)	111 (28.3%)	0.64 [0.41 - 1.00]

CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura ; ALL : All AID combined.

**: Unconditional logistic regression on dematched case-control sets adjusted for age

5.4 Further analyses conducted for identification of bias

In addition to the validity studies presented in paragraph 2 above of this report, a number of checks were made on the data, described below.

5.4.1 Diagnostic bias and case/non case status

In these reports, 'diagnostic bias' refers to systematic misdiagnosis, 'selection bias' refers to systematic differences in the selection of cases and controls, and 'recall bias' refers to systematic differences in the recall of exposures. These biases may be related to the exposure (vaccination with HPV vaccine) or other factors. Measures were taken to minimise all of these forms of bias.

Precautions were taken to minimise diagnostic information bias; all cases were validated through the clinical algorithm for case definition and diagnostic certainty. Altogether, out of the 574 reported in 11-25 year old eligible females, 5 (0.9%) were excluded due to diagnosis. This was explained in all instances by the precocity of the report of the case just after the first symptoms, as

per instruction given to investigators. Further details on diagnostic Issues are exposed with the reports on individual disorders.

Rejected cases were checked for their exposure to HPV. In all, 5 of the 5 rejected cases could be documented for their potential use of HPV vaccine, because they had been interviewed before exclusion or because data had been obtained from their general practitioner on prescriptions. Of them none had such use reported.

Among the 168 centres who participated in the study, 5 different centres recruited each one 1 rejected cases.

5.4.2 Repetition of the general analysis, removing AIT and GBS cases

Table 24 shows the results of the sensitivity analysis which repeated the general analysis, removing AIT and GBS cases separately (for definite and possible cases and any HPV vaccine use before index date). It did not show any significant results from the main analysis.

Table 24. All AIDs combined, removing AIT and GBS cases separately (for definite and possible cases and any HPV vaccine use before index date)

Exposure	Cases n (%)	Controls n (%)	Matched Crude* OR 95% CI	Matched Adjusted** OR 95% CI
Any use before index date – DEFINITE & POSSIBLE CASES				
Excluding AIT cases	**n=404**	**n=1563**		
HPV vaccine	83 (20.5%)	554 (35.4%)	0.58 [0.44 - 0.77]	0.59 [0.44 - 0.80]
Excluding GBS cases	**n=497**	**n=1910**		
HPV vaccine	104 (20.9%)	682 (35.7%)	0.60 [0.46 - 0.77]	0.65 [0.50 - 0.85]

GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis.

* Conditional logistic regression using exposure status

**: Conditional logistic regression on matched case-control sets adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date, number of vaccines other than HPV received within two years before the index date

5.4.3 Other sensitivity analyses

Table 25 shows the results of the sensitivity analyses which repeated the general analysis, in stepping back the index date of one year to further investigate mis information on the index date reported by the recruiting specialists. It did not show any significant results from the general analysis.

Table 25. All AIDs combined and each individual AID, stepping back the index date of 1 year (for definite and possible cases and any HPV vaccine use before index date)

Exposure	Cases n (%)	Controls n (%)	Matched Crude* OR 95% CI	Matched Adjusted** OR 95% CI
1 year step-back of index date – DEFINITE & POSSIBLE CASES				
HPV vaccines use				
CD/MS (116/893)	20 (17.2%)	213 (23.9%)	0.74 [0.42 – 1.30]	0.85 [0.48 – 1.50]
CTD (105/872)	15 (14.3%)	184 (21.1%)	0.64 [0.34 – 1.19]	0.69 [0.34 – 1.39]
GBS (13/130)	1 (7.7%)	19 (14.6%)	0.46 [0.05 – 3.97]	NC
T1D (93/870)	10 (10.8%)	145 (16.7%)	0.58 [0.28 – 1.21]	0.63 [0.29 – 1.34]
AIT (106/876)	19 (17.9%)	205 (23.4%)	0.74 [0.41 – 1.31]	0.92 [0.50 – 1.70]
ITP (77/698)	11 (14.3%)	102 (14.6%)	1.03 [0.50 – 2.11]	1.09 [0.52 – 2.29]
ALL (510/1953)	76 (14.9%)	448 (22.9%)	0.65 [0.48 – 0.88]	0.72 [0.53 – 0.98]

CD/MS : central demyelination/multiple sclerosis ; CTD : Connective tissue disease ; GBS : Guillain-Barre Syndrom ; AIT : autoimmune thyroiditis ; T1D : Type 1 diabetes ; ITP : immune thrombocytopenic purpura ; ALL : All AID combined.

* Conditional logistic regression using exposure status

**: Conditional logistic regression on matched case-control sets adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date, number of vaccines other than HPV received within two years before the index date

Table 26 shows the results of the sensitivity analyses which repeated the general analysis separately in the 2 phases of recruitment; Phase 1 date of first symptoms of cases from April 2008 to April 2011 and Phase 2 date of first symptoms of cases from May 2011 to September 2014.

Table 26. All AIDs combined and each individual AID, separately in Phase 1 and Phase 2 of recruitment (for definite and possible cases and any HPV vaccine use before index date)

Exposure	Cases n (%)	Controls n (%)	Matched Crude* OR 95% CI	Matched Adjusted** OR 95% CI
Phase 1/Phase 2 – DEFINITE & POSSIBLE CASES				
HPV vaccines use				
CD/MS – Phase 1 (64/496)	6 (9.4%)	144 (29.0%)	0.27 [0.11 - 0.67]	0.31 [0.12 - 0.79]
CD/MS – Phase 2 (52/397)	16 (30.8%)	138 (34.8%)	0.95 [0.47 - 1.89]	1.17 [0.57 - 2.41]
CTD – Phase 1 (61/470)	10 (16.4%)	127 (27.0%)	0.57 [0.26 - 1.24]	0.73 [0.32 - 1.69]
CTD – Phase 2 (44/402)	13 (29.5%)	133 (33.1%)	0.83 [0.40 - 1.74]	0.96 [0.41 - 2.26]
GBS – Phase 1 (11/110)	0 (0.0%)	22 (20.0%)	NC	NC
GBS – Phase 2 (2/20)	1 (50.0%)	5 (25.0%)	NC	NC
T1D – Phase 1 (43/403)	11 (25.6%)	112 (27.8%)	0.94 [0.43 - 2.08]	0.95 [0.42 - 2.16]
T1D – Phase 2 (50/467)	6 (12.0%)	101 (21.6%)	0.45 [0.17 - 1.17]	0.53 [0.19 - 1.46]
AIT – Phase 1 (36/330)	3 (8.3%)	73 (22.1%)	0.31 [0.09 - 1.07]	0.34 [0.09 - 1.24]
AIT – Phase 2 (70/546)	19 (27.1%)	204 (37.4%)	0.66 [0.36 - 1.21]	0.81 [0.43 - 1.52]

ITP – Phase 1 (44/394)	13 (29.5%)	110 (27.9%)	1.21 [0.59 - 2.47]	1.24 [0.59 - 2.60]
ITP – Phase 2 (33/304)	7 (21.2%)	85 (28.0%)	0.66 [0.27 - 1.64]	0.69 [0.27 - 1.76]
ALL – Phase 1 (259/1067)	43 (16.6%)	373 (35.0%)	0.54 [0.37 - 0.79]	0.61 [0.41 - 0.91]
ALL – Phase 2 (251/886)	62 (24.7%)	322 (36.3%)	0.63 [0.45 - 0.89]	0.67 [0.47 - 0.96]

CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura ; ALL : All AID combined.

* Conditional logistic regression using exposure status

**: Conditional logistic regression on matched case-control sets adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date, number of vaccines other than HPV received within two years before the index date